The cardiac component of cardiac cachexia

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Background Recent evidence suggests the importance of noncardiac mechanisms in the genesis of the syndrome of cardiac cachexia. This raises the question of the relative role of the heart itself in this syndrome. This study sought to assess the cardiac dimensions, mass, and function and changes in these parameters over time in patients with chronic heart failure with and without cachexia.

Methods Doppler echocardiography was performed in 28 patients with nonedematous weight loss (>7.5% over a period of >6 months) compared with 56 matched patients without weight loss in a ratio of 1:2 (age 71 ± 13 vs 67 ± 8 years, $P = .07$; New York Heart Association class 2.9 ± 0.7 vs 2.6 ± 0.6, $P = .08$). In 18 cachectic and 35 noncachectic patients with previous echocardiographic recordings, we analyzed the changes in left ventricular (LV) dimensions and mass over time.

Results Cardiac dimensions including LV diastolic (69 ± 9 mm vs 67 ± 13 mm) and systolic cavity diameter (58 ± 11 mm vs 55 ± 15 mm), LV mass (480 ± 180 g vs 495 ± 190 g), and LV systolic and diastolic function including fractional shortening (16% ± 10% vs 18% ± 10%), isovolumic relaxation time (29 ± 22 ms vs 36 ± 27 ms), and E/A ratio (2.7 ± 1.6 vs 3.3 ± 2.9) did not differ between cachectic and noncachectic patients (all $P > .1$). By analyzing changes in LV mass over time, we found an increase (>20%) in 2 (11%) cachectic and 14 (40%) noncachectic patients and a decrease in LV mass (>20%) in 9 (50%) cachectic and 8 (23%) noncachectic patients (χ^2 test, $P < .05$).

Conclusions Although no specific cardiac abnormality could be detected echocardiographically in cachectic patients compared with patients with noncachectic chronic heart failure in a cross-sectional study, over time a significant loss of LV mass (>20%) occurs more frequently in patients with cardiac cachexia. (Am Heart J 2002;144:45-50.)

Long-standing severe chronic heart failure (CHF) is often accompanied by a loss of total body fat and lean body mass, known in its most severe form as cardiac cachexia. It has been recognized since the classic description by Hippocrates[1] and is associated with a particularly adverse prognosis.[2] A clear understanding of the mechanisms of reduced weight and wasting occurring in this syndrome still eludes us. A reduced blood flow to the limbs[3,4] may deprive tissues of the necessary substrates for normal protein turnover and growth.[5] The concept of generalized cellular hypoxia as a consequence of the failing heart is thought by some to be of central importance to the pathogenesis of cardiac cachexia.[6] However, growing evidence suggest the importance of noncardiac mechanisms in the genesis of the syndrome. These include malnutrition,[7,8] neurohormonal and immune activation with catabolic-anabolic imbalance,[9] cytokine activation,[10-13] and altered protein, fat, and bone mineral metabolism.[14-16] The increasing evidence of the "peripheral" component of cachexia raises the question of the relative importance of the "central," or cardiac component.

Although the cachectic heart has been described as a pathologic decrease in the size and mass of the heart,[17] no studies have followed changes in cardiac dimensions or mass over time in patients with CHF with cardiac cachexia. The purpose of this investigation was to assess cardiac dimensions, mass, and function and changes in these parameters over time in patients with CHF with and without cachexia by use of quantitative Doppler echocardiographic techniques.

Methods

Patient population and characteristics

The target population for this study was all cachectic patients with CHF of ischemic or dilated cardiomyopathy ori-

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gin, referred for an echocardiographic examination as part of their routine assessment at the Royal Brompton Hospital between 1992 and 1999. A total of 28 male consecutive patients with cardiac cachexia were studied. Cardiac cachexia was defined as documented nonedematous and nonintentional weight loss of >7.5% over a period of >6 months.[2] The diagnosis of heart failure was based on history, examination, electrocardiogram, chest radiography, and echocardiographic findings and made if both of the following were present: symptoms compatible with a diagnosis of heart failure, mainly exertional breathlessness for at least 6 months, and evidence of substantial impairment of left ventricular (LV) systolic function or LV filling on Doppler echocardiography. These patients were matched with 56 patients with CHF without weight loss in a ratio of 1:2. There was no difference between the 2 groups with and without cachexia with respect to the underlying cause of heart failure. Heart failure was of ischemic origin in 18 (64%) cachectic patients and in 37 (66%) noncachectic patients. The presence of ischemic heart disease was shown by coronary arteriography or documented myocardial infarction. Patients were classified as having dilated cardiomyopathy if normal coronary arteries had been demonstrated on coronary angiography. The cachectic group did not differ significantly from the noncachectic group with respect to age (71 ± 13 vs 67 ± 8 years, P = .07) and New York Heart Association class (2.9 ± 0.7 vs 2.6 ± 0.6, P = .08) and had a lower body mass index (21 ± 2 kg/m^2 vs 28 ± 4 kg/m^2, P < .0001).

No patient had uncorrected hemodynamically significant valvular disease, myocardial infarction within the previous 12 weeks, chronic lung disease, neuromuscular disorders, or severe kidney failure. The medical regimens of all the enrolled patients were optimized and all were symptomatically stable. Medications included angiotensin-converting enzyme inhibitors, diuretics, nitrates, digitalis, β-blockers, and aspirin or warfarin in varying combinations. No significant differences in medication were found between cachectic and noncachectic patients.

In the documentation of weight loss for the detection of cachexia, special care was taken that no patient had peripheral or pulmonary edema, significantly elevated jugular venous pressure, hepatomegaly, or ascites at the time of assessment. The noncachectic patients had no history of significant nonedematous weight loss in the 2 years before the study.

Procedures

Simultaneous Doppler echocardiograms and phonocardiograms were recorded along with standard lead II of the electrocardiogram, with the patient supine and in the left semilateral position. All patients were studied at rest and during quiet respiration.

Echocardiograms were recorded with the use of a Hewlett-Packard Sonos 1500 echocardiograph with a 2.5-MHz transducer (Andover, Mass). The pattern of LV wall motion was assessed from standard left parasternal and apical views. Systolic and diastolic LV dimensions, septal thickness, and posterior wall thickness were measured from the M-modes of the LV minor axis obtained with the cursor by the tips of mitral valve leaflets, with the use of leading-edge methodology. End-diastole was taken as the onset of the q wave of the simultaneously recorded electrocardiogram and end-systole as the onset of the aortic component of the second heart sound (A_2) on the phonocardiogram. All Doppler cardiographic recordings were made at a paper speed of 100 millimeters per second. The LV mass was calculated from Penn convention criteria.[18] Left ventricular fractional shortening was estimated as the percentage of decrease in dimension during ejection with respect to end-diastolic dimension. Posterior wall thickening fraction was calculated as the percentage of increase in end-systolic wall thickness with respect to end-diastolic thickness. From the long-axis traces, the total amplitude of long-axis excursion was determined at the left, septal, and right sites, and the mean mitral ring movement was calculated. Left ventricular isovolumic relaxation time was measured as the time interval from the A_2 to the onset of mitral cusp separation on the M-mode trace. From the transmitral pulsed-Doppler trace, peak early (E) and late (A) diastolic filling velocities were measured and the E/A ratio was calculated. Mitral E-wave deceleration time was measured from the peak of the E wave to its end.

Phonocardiograms were recorded from the right or left sternal edge, with the use of a medium- or high-frequency filter, in the position where A_2 was most obvious, checked against aortic valve closure artifact on pulsed Doppler record of aortic flow.

Changes in measurements of LV performance over time

To assess the changes in measurements of LV cavity size, mass, and function over time, before the index assessment, all available previous echocardiographic recordings performed in our laboratory were also analyzed. Eighteen cachectic and 35 noncachectic patients included in the study were identified as having had a previous echocardiographic examination ≥6 months before the index assessment (mean follow-up time 24 ± 15 months). The reproducibility of the echocardiographic overall LV performance in our laboratory has been described previously.[19]

Statistical analysis

Descriptive values are expressed as mean ± SD for cross-sectional parameters and mean ± SEM for changes over time within patients groups. The unpaired Student t test, Mann-Whitney U test, and χ^2 test were used when appropriate. For all tests, a P value of <.05 was considered statistically significant. The reproducibility of LV mass assessments with the use of echocardiography is limited. Therefore, for the assessment of changes over time in LV mass, we focused on the determination of a definite state of LV mass increase (>20%) or a state of LV mass decrease (>20%). Statistical analysis was performed with a standard statistical program package (StatView, version 4.5, Abacus Concepts Inc, Berkely, Calif).

Results

Chamber size, dimensions, and systolic function

Left ventricular and left atrial size did not differ between the 2 groups, although LV dimensions were

Table I. M-mode echocardiographic measurements and left ventricular systolic function in the two patient groups with and without cardiac cachexia (mean ± SD)

	Cachectic (n = 28)	Noncachectic (n = 56)	P
Left ventricular end-diastolic diameter (mm)	69 ± 9	67 ± 13	.43
Left ventricular end-systolic diameter (mm)	58 ± 11	55 ± 15	.35
Interventricular septal thickness (mm)	12 ± 3	13 ± 3	.11
Left ventricular posterior wall thickness (mm)	11 ± 2	12 ± 2	.4
Left ventricular mass (g)	480 ± 180	495 ± 190	.73
Left atrial dimension (mm)	48 ± 9	46 ± 8	.56
Left ventricular fractional shortening (%)	16 ± 10	19 ± 10	.23
Left ventricular posterior wall thickening (%)	53 ± 19	60 ± 15	.37
Mean mitral ring movement (mm)	8 ± 3	9 ± 3	.25

Table II. Left ventricular diastolic function in the two patient groups (mean ± SD)

	Cachectic (n = 28)	Noncachectic (n = 56)	P
M-mode measurements			
Isovolumic relaxation time (ms)	29 ± 22	36 ± 27	.26
Doppler measurements			
Peak E diastolic filling velocity (m/s)	0.7 ± 0.3	0.8 ± 0.3	.71
Peak A diastolic filling velocity (m/s)	0.4 ± 0.2	0.4 ± 0.3	.86
E/A ratio	2.7 ± 1.6	3.3 ± 2.9	.31
E-wave deceleration time (ms)	73 ± 37	76 ± 26	.77

slightly greater in the cachectic patients (Table I). Minimal differences were found in interventricular septal thickness ($P = .11$) and posterior ($P = .40$) wall thickness and LV mass between the 2 groups with and without cachexia, but LV mass was almost identical in both study groups ($P = .73$). Similarly, LV function assessed by percent fractional shortening, the rate of posterior wall thickening, and the mean mitral ring movement did not differ. Left ventricular fractional shortening was lower (16% ± 10% vs 19% ± 10%) in patients with cardiac cachexia, but this difference did not achieve statistical significance ($P = .23$). This lower average value was due to slightly greater end-diastolic and end-systolic diameters among the cachectic patients and not to markedly lower values for percent fractional shortening in a few subjects.

Diastolic function

Left ventricular diastolic function assessed by the Doppler pattern of LV inflow and E-wave deceleration time was also similar in the cachectic and noncachectic groups (Table II). Isovolumic relaxation time was slightly lower in cachectic patients (29 ± 22 ms vs 36 ± 27 ms), indicating that left atrial pressure and LV filling pressure were slightly higher in these patients. Nevertheless, this difference was statistically nonsignificant ($P = .26$), and no other variables suggested specific diastolic abnormalities in patients with cardiac cachexia.

Changes in measurements of LV performance over time

There were no consistent changes in LV size, mass, and function from the previous examination to the index examination in the patient population as a whole, though the direction of changes differed between cachectic (n = 18) and noncachectic (n = 35) patients (Table III). Although the measurements of LV size and mass remained stable or slightly increased during the time interval between the previous and index examinations in the noncachectic group, these variables had a consistent negative direction in the cachectic group (Table IV). The differences in change over time between the groups with and without cachexia achieved statistical significance in terms of LV end-diastolic diameter and were the strongest for changes in LV mass (Figure 1). By focusing on the determination of definite LV mass increase (>20%) or a state of definite LV mass decrease (>20%), we found an increase in LV mass in 2 (11%) cachectic and 14 (40%) noncachectic patients, stable LV mass in 7 cachectic and 13 noncachectic patients, and a decrease in LV mass in 9 (50%) cachectic and 8 (23%) noncachectic patients (χ^2 test, $P < .05$).

Table III. Measurements of left ventricular cavity size and mass at index and previous examinations and absolute changes in variables during time interval between the two examinations (mean ± SEM)

	Previous examination	Index examination	Absolute changes
LVEDD (mm)			
Cachectic	73 ± 2	68 ± 3	−5 ± 2
Noncachectic	64 ± 2	66 ± 2	1 ± 2
LVESD (mm)			
Cachectic	62 ± 3	58 ± 3	−4 ± 2
Noncachectic	53 ± 2	52 ± 2.	1 ± 2
IVST (mm)			
Cachectic	12.4 ± 0.5	12.4 ± 0.6	0.1 ± 0.6
Noncachectic	12.5 ± 0.4	12.8 ± 0.4	0.4 ± 0.4
LVPWT (mm)			
Cachectic	11.3 ± 0.4	10.6 ± 0.6	−0.7 ± 0.5
Noncachectic	11.3 ± 0.3	11.3 ± 0.3	0.1 ± 0.3
LV mass (g)			
Cachectic	540 ± 45	455 ± 40	−80 ± 45
Noncachectic	430 ± 25	460 ± 30	35 ± 25

LV, Left ventricular; *LVEDD*, LV end-diastolic dimension; *LVESD*, LV end-systolic diameter; *IVST*, interventricular septal thickness; *LVPWT*, LV posterior wall thickness.

Table IV. Percent changes in measurements of left ventricular cavity size and mass during time interval between previous and index examinations (mean ± SEM)

	Cachectic (n = 18)	Noncachectic (n = 35)	p
Left ventricular end-diastolic diameter (%)	−6 ± 3	3 ± 3	<.05
Left ventricular end-systolic diameter (%)	−6 ± 3	3 ± 5	.2
Interventricular septal thickness (%)	1 ± 5	5 ± 4	.53
Left ventricular posterior wall thickness (%)	−6 ± 4	2 ± 3	.12
Left ventricular mass (%)	−11 ± 7	11 ± 6	<.03

Discussion

The current study failed to detect any specific cardiac abnormalities in patients with cachectic CHF compared with patients with noncachectic CHF when assessed in a cross-sectional study. Neither measurements of cardiac dimensions and mass nor measurements of LV systolic and diastolic function differed significantly between the 2 study groups with and without cachexia. However, when these patients were followed for a mean of 24 months, changes in ventricular mass and transverse cavity diameter were observed, which differed in direction in patients with cardiac cachexia compared with noncachectic patients. In the group of patients as a whole, none of the measurements showed any significant change. Nevertheless, in individuals, a significant loss of LV mass over time occurred more frequently in cachectic patients compared with noncachectic patients, strongly suggesting that neither change was simply random or the result of measurement error but rather that such continuous evolution should be considered as part of the natural history of the disease.

Previous studies

The phenomenon of cardiac cachexia has been recognized for many centuries.[1] The entity "cachectic heart," first described in 1968 by Burch et al[17] as an acquired pathologic decrease in size, mass, and fat content of the heart, was of central importance in explaining the pathogenesis of cardiac cachexia. The role of reduced blood flow to the tissues was further developed by Pittman and Cohen,[6] who proposed that generalized cellular hypoxia is of central importance to the pathogenesis of the syndrome of cardiac cachexia. It results in poor oxidative metabolism in muscle with subsequent reduced ATP production that depresses protein synthesis.[20] They also suggested that cellular hypoxia initiates catabolism or inhibits anabolism.[6]

Several subsequent studies questioned the importance of the changes in the heart itself in the genesis of cardiac cachexia, indicating the role of severe anorexia[21] and of altered lipid metabolism.[22] Ansari[23] described 2 different syndromes of cardiac cachexia and of the cachectic heart. He also proposed the presence of pedal edema, cardiac size, and QRS voltage on

serial electrocardiography as the most important clues in the differential diagnosis of these 2 syndromes.[23] The syndrome of cardiac cachexia within CHF has subsequently received little attention.[24]

Current studies

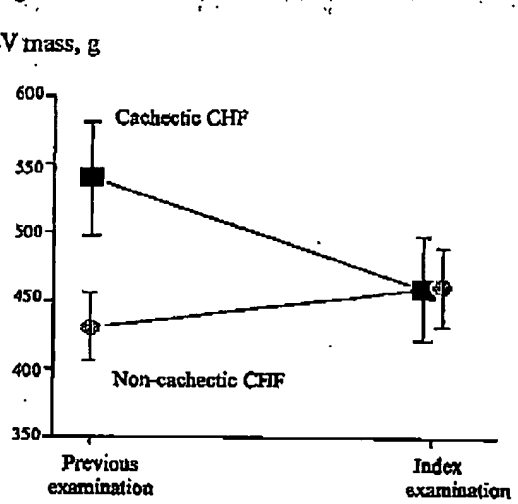
Although the reasons for loss of muscle remain unclear, CHF is regarded as a catabolic state with cytokine production,[10-13,25,26] insulin resistance,[27] and an abnormal ratio of catabolic to anabolic steroids.[28] The syndrome of cardiac cachexia is currently shown to be closely related to neurohormonal activation[9] and metabolic alterations.[14-16,29] The increasing evidence of these "noncardiac" factors raise the question of the importance of alterations in cardiac structure and function in this syndrome.

Current study

It is generally accepted that worsening of heart failure is associated with an increase in LV size and mass, and this is confirmed in our noncachectic subgroup of patients. Whether this can be expanded to cachectic heart failure has not been investigated previously. In our study, no significant differences in LV mass were found between cachectic and noncachectic patients both at the time of previous examination and of index examination. However, when monitoring these patients, significant difference in changes in this variable over time were noticed. Although echocardiography has some limitations in estimating LV mass, this difference was proved by the significant difference in changes over time in LV diastolic cavity diameter and by the observed trend in differences in changes over time in the ventricular posterior wall thickness (Table IV). The logical time sequence of events to explain these findings can be that the patients were analyzed at the time when noncachectic patients on average would still have an increase in LV mass over time and cachectic patients were on average loosing LV mass.

The pathogenesis of cardiac cachexia has yet to be elucidated, and the role of the heart in this syndrome remained obscure until evidence emerged that cachectic patients have high circulating levels of tumor necrosis factor.[10] This cytokine causes many of the clinical features of cachexia, and its production is increased in patients with a variety of neoplastic, infective, and collagen disorders characterized by muscle wasting and malnutrition.[30] In the study of Ansari,[23] the syndrome of cachectic heart was described apart from the syndrome of cardiac cachexia, implying different pathogenetic mechanisms in these syndromes. In our study, the reduction in body weight occurred in parallel to the wasting of LV mass, indicating a common mechanism. Possibly, the neurohormonal activation[31] that accompanies the failing heart could induce a variety of "peripheral" alterations, including abnormalities of the skeletal muscle and metabolic impairment. When the sum of these factors reach a threshold, a cascade of secondary vicious circles are initiated, leading to skeletal and cardiac muscle wasting and cachexia.

Figure 1



Dynamics of left ventricular mass over time in patients with and without cachexia. ΔLV mass in cachectic patients versus ΔLV mass in noncachectic patients, $P < .03$.

Limitations

Retrospective data were used to assess the changes in measurements of LV performance over time, though all measurements were performed by a single experienced observer who was unaware of patient details and group assignment. The individual measurements we made, particularly in LV cavity size and mass, will have been subject to measurement error, a problem compounded when small differences between those made on 2 occasions several months apart were derived. This effect was minimized by use of identical equipment and techniques on both occasions. Although all patients were receiving standard medications, treatment was individualized and was thus not uniform throughout the group of patients studied, and most of the patients were studied before β-blockers were included in standard therapy. We are thus unable to determine whether their use would have altered dynamics of LV size and mass over time. Finally, measurements in individual patients were made on only 2 occasions, so we cannot say whether these changes

are consistent or subject to longer-term variability in their direction or magnitude.

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References

1. Katz AM, Katz PB. Diseases of heart in works of Hippocrates. Br Heart J 1962;24:257-64.
2. Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999; 115:836-47.
3. Wilson JR, Martin JL, Schwartz D, et al. Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. Circulation 1984;69:1079-87.
4. Clark A, Valterrani M, Swan JW, et al. Leg blood flow, metabolism and exercise capacity in chronic stable heart failure. Int J Cardiol 1996;55:127-35.
5. Gibson JN, Halliday D, Morrison WL, et al. Decrease in human quadriceps muscle protein turnover consequent upon leg immobilisation. Clin Sci 1987;72:503-9.
6. Fitman JA, Cohen P. The pathogenesis of cardiac cachexia. N Engl J Med 1964;271:403-8.
7. Abel RM, Fisher J, Buckley MJ, et al. Malnutrition in cardiac surgical patients. Arch Surg 1976;111:45-50.
8. Carr JG, Stevenson LW, Walden JA, et al. Prevalence and hemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1989;63:709-13.
9. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997;96:526-34.
10. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236-41.
11. McMurray J, Abdullah I, Dargie HJ, et al. Increased concentrations of tumor necrosis factor in "cachectic" patients with severe chronic heart failure. Br Heart J 1991;66:356-8.
12. Anker SD, Egerer KR, Volk HD, et al. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol 1997;79:1426-30.
13. Dutka DP, Elborn JS, Delamere F, et al. Tumor necrosis factor in severe congestive cardiac failure. Br Heart J 1993;70:141-3.
14. Rauchhaus M, Carroll PV, Russel-Jones D, et al. Body wasting in chronic heart failure is associated with altered fat and protein metabolism [abstract]. J Am Coll Cardiol 1999;33(A Suppl):171.
15. Leyva F, Anker SD, Egerer K, et al. Hyperleptinaemia in chronic heart failure, relationships with insulin. Eur Heart J 1998;19:1547-51.
16. Anker SD, Clark AL, Teixeira MM, et al. Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 1999;83:612-5.
17. Burch GE, Phillips JH, Ansari A. The cachectic heart, a clinicopathologic, electrocardiographic and roentgenographic entity. Chest 1968;54:403-9.
18. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1979;59:623-32.
19. Henein MY, Amadi A, O'Sullivan C, et al. ACE inhibitors unmask incoordinate diastolic wall motion in restrictive left ventricular disease. Heart 1996;76:326-31.
20. Morrison WL, Gibson NA, Rennie MJ. Skeletal muscle and whole body protein turnover in cardiac cachexia: influence of branched chain amino acid administration. Eur J Clin Invest 1988;75:415-20.
21. Buchanan N, Keen RD, Kingsley R, et al. Gastrointestinal absorption studies in cardiac cachexia. Intensive Care Med 1977;3:89-91.
22. Bobkova VI, Fomchenkov SI. Pathogenesis of cachexia in cardiac insufficiency [in Russian]. Kardiologiia 1975;15:22-5.
23. Ansari A. Syndromes of cardiac cachexia and the cachectic heart: current perspective. Prog Cardiovasc Dis 1987;30:45-60.
24. Ferrari R. The importance of cachexia in the syndrome of heart failure [editorial]. Eur Heart J 1997;18:187-9.
25. Zhao SP, Zeng LH. Elevated plasma levels of tumor necrosis factor in chronic heart failure with cachexia. Int J Cardiol 1997;58:257-61.
26. Doyama K, Fujiwara W, Fukumoto M, et al. Tumour necrosis factor is expressed in cardiac tissues of patients with heart failure. Int J Cardiol 1996;54:217-25.
27. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relationship to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527-30.
28. Anker SD, Clark AL, Kemp M, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. J Am Coll Cardiol 1997;30:997-1001.
29. Morrison WL, Edwards RHT. Cardiac cachexia. BMJ 1991;302: 301-2.
30. Packer M. Is tumor necrosis factor an important neurohormonal mechanism in chronic heart failure? Circulation 1995;92:1374-82.
31. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248-54.